REMARKS

Claims 1-5 are pending in the application, claim 6 being cancelled herein. Claims 1 and 5 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. The amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 1, support for the recited polymorphisms in linkage disequilibrium with the DRD4-7R allele can be found throughout the specification. For example, see Figure 3 and the specification at pages 11-12.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Action rejected all of the claims under 35 U.S.C. §112. Applicants traverse all rejections and objections, to the extent that they are applied to the amended claims.

35 U.S.C. §112 ¶1 – WRITTEN DESCRIPTION

Claims 1-6 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. To the extent that these rejections are applied to the amended claims, Applicants traverse.

The "written description" requirement has been formulated in a number of ways over the years. One relatively clear, current and concise statement of the written description requirement set forth by the Federal Circuit is as follows:

> "The [written description] requirement may be satisfied if the claim terms 'readily convey distinguishing information concerning their identity, such that one of ordinary skill in the art could visualize or recognize the identity of a member of the genus." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQD2d 1385 (Fed. Cir. 2003).

The Action alleges that "a marker having a locus within a block of linkage disequilibrium surrounding a DRD4 7R allele," as recited in previously presented claim 1, constitutes a genus for which a representative number of species were not adequately

disclosed in the specification. In order to facilitate prosecution, and without acquiescing or agreeing with any rejection of record, independent claim 1 has been amended to include the limitation that testing a human patient for ADHD status comprises testing for one or more of the polymorphisms that the Action helpfully indicated are adequately described in the specification. *See* Action at p. 4 (the genus "is represented in the specification by three named polymorphisms for which data is provided, namely the promoter polymorphism (L1/S1), exon 1 (L2/S2) and intron 3 (G-G/A-C) polymorphisms."). Because the specification provides a precise description of each polymorphism recited in amended claim 1, the written description requirement is clearly met. Accordingly, the rejection should be withdrawn.

35 U.S.C. §112 ¶1 – ENABLEMENT

Claims 1-6 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. To the extent that these rejections are applied to the amended claims, Applicants traverse.

To be an enabling disclosure under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. See *In re Wands*, 8 USPQD2d 1400, 1404 (Fed. Cir. 1988).

The Predictability or Unpredictability of the Art

The Action raises several issues with regard to predictability. First, the Action cites Tantillo et al. as evidence that boys and girls with ADHD respond differently to a given stimulus. *See* Action at p. 9. Applicants note that the claimed invention is directed to evaluating the level of *dopamine release* in response to a particular stimulus. The findings of Tantillo et al. "*suggest* an interaction between sex and exercise intensity," but only as it relates to the rate of spontaneous eye blinks, acoustic startle eye blink response (ASER) and motor impersistence. Tantillo et al. provides no evidence that girls with ADHD will fail to exhibit the effects observed in boys with respect to dopamine release in response to a stimulus. Accordingly, the findings of Tantillo et al. are irrelevant to the predictability of the claimed invention.

Next, the Action cites a study relating to the *treatment* of ADHD with yoga as the basis for asserting that "not all stimuli are statistically associated with treatment and non-treatment groups." *See* Action at p. 9, citing "The effects of yoga on ADHD" by Martin. The present invention is directed to the determining ADHD *status*, in part by evaluating the level of *dopamine release* in response to a stimulus. That yoga purportedly does not produce a therapeutic effect in children with ADHD is irrelevant to the enablement of the claimed invention. The Martin study does not involve any comparison between non-ADHD children and children with ADHD, a necessary methodology for any study relevant to determining ADHD *status*. Rather, the study concerns only treatment and non-treatment groups of children *with ADHD*. In addition, contrary to the Action's conclusion that Martin teaches "yoga . . . is not correlated with dopamine levels" (See Action at p. 18), Martin did not assess dopamine levels in the study's participants. Because Martin bears no relevance to the claimed invention, Applicants find the argument based on Martin unpersuasive.

The Action cites Bhaduri as the basis for concluding "there is no description of markers surrounding the DRD4 7R allele which are within linkage disequilibrium and are associated with ADHD" because Bhaduri "teaches the alleles of 12bp duplication are not associated with ADHD." *See* Action at p. 10. First, Applicants note that Bhaduri describes its findings with respect to a lack of association between ADHD and the exon 1 12 bp duplication as "*preliminary data*." *See* Bhaduri, Abstract. The Action's reliance on preliminary data as indicating the absence of an association between the 12 bp polymorphism and ADHD is odd, particularly in light of Examiner's apparent skepticism with respect to the reproducibility of association studies (see below). Applicants note that, in contrast to the preliminary data used to determine a lack of association between the 12 bp polymorphism and ADHD, Bhaduri reports a statistically significant association between the DRD4-7R allele and ADHD. *See* Bhaduri, Abstract. Moreover, Applicants have shown beyond reasonable statistical doubt that the polymorphisms recited in the amended claims (including the exon 1 12 bp duplication) exhibit strong linkage disequilibrium with the DRD4-7R allele. *See* Specification at pp. 11-12. Indeed, the Action acknowledges Applicants' demonstration of strong LD between the recited polymorphisms and the 7R allele. *See* Action at p. 7. These polymorphisms are highly predictive of the 7R allele, and the 7R allele, in turn, exhibits a strong association with ADHD. Bhaduri presents no credible evidence to refute the predictability of utilizing the recited polymorphisms to determine ADHD status.

Further, the Action calls into question the reproducibility of association studies generally. The association data presented by Applicants in the specification is the result of a massive *confirmatory* study involving the sequencing of **600** chromosomes in which **56** different haplotypes

and 35 distinct DRD4-7R alleles were identified. This is clearly not the type of association study that raises the reproducibility issues discussed in Hirschhorn and Ioannidis, and the Action's calling into question the validity of Applicants' statistically significant, peer-reviewed findings is improper.

The Action cites Meyer et al. for the proposition that "the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease." It is unclear how this proposition supports the conclusion that the claimed invention lacks enablement, because *the invention actually exploits this principle*. Applicants have identified numerous polymorphisms in DRD4, and they have determined that certain polymorphisms, e.g., those cited in claim 1, exhibit strong LD with DRD4-7R, the allele of DRD4 associated with ADHD. It is for the very reason that not every polymorphism in DRD4 is associated with DRD4-7R (or ADHD) which renders the polymorphisms recited in the claimed invention highly predictive of the disorder. No aspect of the claimed invention is in conflict with the proposition set forth in the Action that not every polymorphism within a gene will be associated with a disease/disorder. Accordingly, Meyer et al. is irrelevant for determining whether Applicants' disclosure is enabling.

Guidance in the Specification

The Action alleges that guidance in the specification is inadequate. For the reasons that follow, Applicants assert that the guidance in the specification is more than adequate to enable one of skill in the art to practice the claimed invention.

First, the Action states that "the level of dopamine is statistically different only in response to exercise at the peak time following the baseline measurement." *See* Action at p. 11. This reasoning is unpersuasive. The specification provides a detailed protocol for determining ADHD status that includes identifying individuals that exhibit altered dopamine release in response to a stimulus, e.g., exercise. That the altered dopamine response is not apparent throughout the *entire* course of the protocol does not support a conclusion that the claimed invention lacks enablement. When one of skill reads the disclosure and wishes to practice the claimed invention, he/she can, e.g., assess dopamine levels at the peak time following baseline measurement; it is at this time point where Applicants disclose a statistically significant difference in dopamine response in individuals with ADHD as compared to non-ADHD individuals.

The Action also states that the dopamine release study provides "no indication of the 7R allele status of the various patients." Applicants reiterate (from the response to the first Office Action) that the claimed invention constitutes a two-pronged approach for determining ADHD status. The rationale of this approach is set forth at, e.g., the specification at p. 4. The genetic test acts as a screen to identify false positives, e.g., non-ADHD children who exhibit behavioral excesses that are

distinct, but difficult to discern from the cognitive/behavioral phenotypes of ADHD. The dopamine release test is employed to confirm that individuals who tested positive for the genetic features associated with ADHD actually exhibit the neurochemical deficits that underlie the "true" disorder. The disclosed exercise protocol constitutes a definitive tool for differentiating individuals who possess the "true" neurochemical ADHD phenotype from those who do not. In accordance with the claimed invention, this test will be conducted on individuals who test positive for the 7R allele, as indicated by the presence of one or more of the recited polymorphisms.

The Quantity of Experimentation

With respect to the quantity of experimentation, the Action alleges: it is unpredictable whether females will respond similarly to the exercise protocol as compared to males; that the specification teaches different 7R allele frequencies among ethnic groups; and which levels of dopamine are indicative of ADHD status. Undue experimentation is not required to practice the claimed invention, for the reasons that follow.

The Action cites no art to suggest a differential dopamine release response to the disclosed exercise protocol in girls as compared to boys. As noted above, Tantillo did not assess dopamine levels in response to exercise. Even if ADHD positive girls do not exhibit – as compared to those who are ADHD negative – the differential release of dopamine in response to, e.g., the protocol disclosed in the specification (which Applicants do not concede), Applicants disclosure is enabling for a sufficient portion of the genus (males, approximately 50% of the genus) to warrant the conclusion that the genus of the claimed invention is enabled.

The Action asserts that the specification teaches a variation in 7R alleles across ethnic groups. *See* Action at p. 12. While Applicants describe a modest variation in the frequency of 7R *haplotypes* across certain ethnic groups, this is not related to the statistically significant finding that the 7R allele is associated with ADHD. In addition to the data provided in Applicants' disclosure, Badhuri describes variation in haplotype frequencies across ethnic subpopulations in India, but nonetheless found that the "7 repeat alleles of exon 3 48-bp VNTR showed significant association with ADHD." *See* Bhaduri, Abstract. Thus, a variation in 7R alleles across ethnic groups does not refute the association observed by numerous independent investigators between the 7R allele and ADHD.

The Action asserts that undue experimentation would be required to determine the levels of dopamine indicative of ADHD status, because the specification "fails to provide any guidance which levels are indicative of ADHD and normal individuals." *See* Action at p. 13. The dopamine release study indicates that dopamine levels in the ADHD group *did not change*, whereas a

significant increase was observed in the control group. *See* Specification at p. 21. Therefore, knowledge of a specific level of dopamine release in ADHD and non-ADHD individuals is not required to practice the claimed invention. Rather, the *absence of an increase* in dopamine release is indicative of ADHD status, while an increase in dopamine release is indicative of non-ADHD status. Moreover, Figure 3 provides distinct ranges of dopamine levels (pg/ml) between ADHD and non-ADHD individuals that one of skill can use as a guide for determining an individual's ADHD status. Either of these analytical approaches (or a combination thereof) for determining ADHD status is well within the grasp of one of skill in the art for practicing the claimed invention.

For these reasons as well as the reasons of record, the rejection must be withdrawn.

35 U.S.C. §112 ¶2 – INDEFINITENESS

Claims 1-6 were rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. To the extent that these rejections are applied to the amended claims, Applicants traverse.

The Action alleges that claim 1 was indefinite for reciting "a marker having a locus within a block of linkage disequilibrium surrounding a DRD4 7R allele . . . ." In amended claim 1, the language that allegedly rendered the claim indefinite has been removed.

The Action also alleges that claim 1 is indefinite because "the claims are unclear how to test for ADHD status." The rationale for determining ADHD status is set forth throughout the specification. *See*, e.g., the specification at p. 4. The claimed method accurately reflects the approach set forth in the specification. The method comprises testing for the presence or absence of one or more of the recited polymorphisms in LD with DRD4-7R, and evaluating the level of dopamine release in the patient in response to a stimulus. The specification teaches that the A and/or C polymorphisms of the A-C SNP pair, as well as the L1 and/or L2 polymorphisms in the DRD4 promoter and DRD4 exon 1, respectively, are indicative of 7R allele, and hence ADHD, status. The specification also teaches that the absence of an increase in dopamine release in response to a stimulus is indicative of ADHD status. One who has read the specification will readily recognize the subject matter to which claim 1 is directed. Accordingly, the rejection for indefiniteness should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 50-0893.

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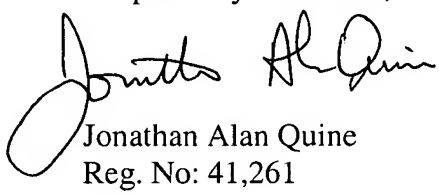
Respectfully submitted,



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Attachments:

1) A transmittal sheet;
2) A receipt indication postcard.